The anti-inflammatory effects of ketamine: state of the art

S. LOIX (*), M. DE KOCK (**) and P. HENIN (*)

Abstract: Inflammation is a major component in keeping the body in homeostasis. However, an overwhelmed inflammatory response may be associated to a loss of this homeostatic status, which may lead to tissue injury or organ dysfunction. A huge number of drugs interacts with the inflammatory response in a positive, negative or “dual” manner. Among these drugs, ketamine seems to have a significant positive effect on the regulation of inflammation. This NMDA-receptor antagonist acts at different levels of inflammation, interacting with inflammatory cells recruitment, cytokines production, and inflammatory mediators regulation. The resultant effect of these interactions confers to ketamine an anti-inflammatory effect by limiting exacerbation of systemic inflammation without affecting local healing processes. This review makes a complete overview of the immunomodulatory properties of this complex anesthetic substance.

Key words: Ketamine; inflammation; cytokin.

The human body evolves constantly in an environment which is sometimes friendly, sometimes hostile. Survival is based on the principle of keeping the body in an homeostatic state. Each aggression for environmental change compels the body to move to a new state of equilibrium compatible with survival. The immune system is a major actor in keeping homeostasis. It plays a great role in detecting and reacting to any environmental change that the body undergoes. By this, it contributes to the adaptive response to stress, described by Hans Selye in the years forty (1).

Inflammatory response caused by aggression makes defending and healing processes possible (fever, pathogenic eradication, wound healing, memory of aggression, ...). However, an overwhelmed activation of immunity is followed by harmful secondary effects. Most of the complications seen after injury (SIRS, ALI, ARDS, TRALI, ...) are the consequences of an uncontrolled inflammatory response. Moreover, complications of a septic state are often due to inflammation itself. SUNTHARALINGAM et al. (2) illustrate this by injecting an inflammatory mediator to healthy volunteers. They observed the same complications as those seen in the setting of severe septic states. This study illustrates the paradoxal effect of an excessive inflammatory response.

Adequate balance of the immune response to homeostatic changes is crucial. It implies a meticulous regulation. As most of the great systems of the human body, the immune system is made of two opposite forces competing against each other. There is a pro-inflammatory and an anti-inflammatory component. The association of these two actors define the extent of the inflammatory response. This drastically simplified system is complicated by a lot of feedback loops modulating the immune response in space and time. The huge variability of stimuli that can be undergone by the body implies that the immune response is initially non specific, which is called the innate immunity. In a second phase, there is a memory of the aggression, which will lead to a specific response if needed. This is the adaptive immunity.

In order to keep the response to stress as accurate as possible, the immune system is under the influence of other entities like the autonomic or endocrine system. Once stimulated, the immune response generates a modulation of these systems, which opens out into new feedback loops, guiding the body to a new equilibrium (Fig. 1).

As explained previously, inflammation is mandatory in the processes of keeping homeostasis following body aggression. Locally, inflammation makes wound healing and pathogen eradication possible while controlling tissue injury. Systemically, an overactive inflammatory response may have severe consequences. This review makes a complete overview of the immunomodulatory properties of this complex anesthetic substance.

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possible. Its inhibition can alter these functions. Besides these local effects, there is a systemic activation of inflammation, which is associated with tissue damage and harmful complication if overwhelmed.

This duality between local and general effects is highly relevant. In order to optimize the immune function, it would be suitable to preserve local healing processes (cicatrisation and pathogen eradication) and to inhibit the excessive systemic reactions and its harmful consequences.

A lot of drugs interact with the immune system, with a wide and complex range of effects. Among them, one drug seems to have a strictly inhibiting effect on the generalisation of inflammation, without impeding with local processes. This drug is called ketamine.

**KETAMINE IN A FEW WORDS**

Ketamine is a phencyclidine derived drug, discovered in the early sixties. It is a dissociative anesthetic. Of a pharmacological point of view, ketamine interacts with a huge number of receptors (Table 1) and ionic channels. The main action of this drug is due to it antagonism of the NMDA receptor. It exerts also a direct action on the morphinic and cholinergic receptors. Ketamine also interacts indirectly with the catecholaminergic receptor by stimulating the release of catecholamines and inhibiting their reuptake. The effect of ketamine on the adenosine receptor will also be discussed later.

The cardiovascular and respiratory properties of ketamine are used for a long time in the setting of critical medical situations. In this context, positive effects of ketamine on morbidity and mortality are described since the middle of the seventies (3, 4). Ketamine optimises peripheral circulation and promotes a better balance between transport and consumption of oxygen. But, since the middle of the eighties, other properties of ketamine have been discovered. In the presence of inflammation, ketamine seems to have immunomodulatory properties. This review makes a complete overview of these interesting properties.

**THE IMMUNE RESPONSE**

To clearly understand the immune response, differences must be made between local and systemic processes:

Each aggression the human body undergoes starts at a local level by disrupting the natural barrier (skin, intestine mucosa, mucus,...). This first step is followed by the activation of local inflammatory cells. Each aggressive process is recognized by macrophages. These cells activate the inflammatory process by liberating mediators called cytokins. Pro-inflammatory cytokins act by spreading the inflammatory signal, attracting neutrophils to the site of aggression. In situ, the activated neutrophils exert their bactericide activity by phagocyting foreign bodies, releasing free radicals and liberating new cytokines.

Beside these local processes, the cytokine network promotes also systemic changes: Platelets are activated by cytokines and promote neutrophils diapedesis by forming microthrombi. Production of circulating leucocytes is enhanced, monocytes undergo changes to become mature macrophages. Cytokins also influence other systems (endocrine and autonomic system), in order to adapt the body to the disturbances caused by aggression.

The whole inflammatory process is regulated by the production of anti-inflammatory cytokines. The resultant of pro- and anti-inflammatory cytokins modulates the inflammatory response in space and time in order to facilitate healing processes and recovery of homeostasis.

This is a brief summary of what is called the aspecific or innate immune response (Fig. 2). There is also a specific immune response based on the production of antigen-specific antibodies. In this setting, macrophages present pathogenic antigens to lymphocytes which produce specific antibodies. This is the specific or acquired immune response.
Ketamine influences the inflammation caused by innate immunity at different levels. We will try to resume these interactions by following the usual process of inflammation in this context.

The first cell to be stimulated by aggression is the macrophage. Macrophages act by producing inflammatory mediators (cytokines and nitric oxide), phagocytising pathogens, and releasing oxidative substances. The effects of ketamine on these functions have been described in several in vitro studies. Ketamine inhibits cytokine production (IL-6 and TNF-α) and nitric oxide production in preparations of isolated and immunostimulated macrophages (5, 6, 7, 8). Moreover, the oxidative function of

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**Table 1**

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Type</th>
<th>Action</th>
<th>Direct/indirect</th>
<th>Effect</th>
<th>Affinity (NMDA = 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholinergic</td>
<td>muscarinic</td>
<td>antagonism</td>
<td>direct</td>
<td>Bronchodilatation hemodynamic</td>
<td>0.05, 0.3</td>
</tr>
<tr>
<td></td>
<td>nicotinic</td>
<td>antagonism</td>
<td>direct</td>
<td>potentiate muscle relaxant sedation</td>
<td></td>
</tr>
<tr>
<td>Opioid</td>
<td>µ &lt; k &lt; δ</td>
<td>direct</td>
<td></td>
<td>analgesia (weak)</td>
<td>0.05 to 0.1</td>
</tr>
<tr>
<td>Glutamate</td>
<td>NMDA</td>
<td>antagonism</td>
<td>direct</td>
<td>Sedation antihyperalgesic anticonvulsivant Neuroprotection</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>AMPA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kainate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GABA</td>
<td></td>
<td></td>
<td>direct</td>
<td>Inhib. of neurotransmission</td>
<td>0.05 to 0.1</td>
</tr>
<tr>
<td>Catecholamine</td>
<td></td>
<td>agonist</td>
<td>indirect</td>
<td>stim. cardiovascular function</td>
<td></td>
</tr>
<tr>
<td>Adenosine</td>
<td></td>
<td>agonist</td>
<td>unknown</td>
<td>immunomodulation</td>
<td></td>
</tr>
</tbody>
</table>

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**Fig. 2. — Innate immunity:** macrophages acts as sensors by recognizing aggressive processes. By producing cytokines, they initiate the immune response. Neutrophils are attracted out of the capillaries and join sites of aggression. Neutrophils release their bactericidal content and produce other cytokines which modulate immune response in space and time. Ketamine interacts with the immune response at different levels (annotated in white).

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**INFLUENCE OF KETAMINE ON INNATE IMMUNITY**

Ketamine influences the inflammation caused by innate immunity at different levels. We will try to resume these interactions by following the usual process of inflammation in this context.

The first cell to be stimulated by aggression is the macrophage. Macrophages act by producing inflammatory mediators (cytokines and nitric oxide), phagocytising pathogens, and releasing oxidative substances. The effects of ketamine on these functions have been described in several in vitro studies. Ketamine inhibits cytokine production (IL-6 and TNF-α) and nitric oxide production in preparations of isolated and immunostimulated macrophages (5, 6, 7, 8). Moreover, the oxidative function of
macrophage is also inhibited which means that ketamine not only inhibits the signalling function of the macrophage but also their bactericidal function (9).

The influence of ketamine on the cytokine network will be discussed later.

The next cell active in the inflammatory process is the neutrophile. Neutrophils play a major role in inflammation, which can be resumed as follows: production of new cytokins, free radicals, and pathogen phagocytosis. Ketamine inhibits these functions. In animal studies based on isolated preparations of neutrophils, ketamine inhibits the production of free radicals (10) and cytokins (11). These inhibitory effects have also been observed in vivo, by using a blood preparation issued from healthy human volunteers (12). The phagocytotic function of neutrophils is also inhibited by ketamine (13).

Moreover, ketamine limits neutrophil diapedesis to the site of inflammation (14, 15, 16). The underlying mechanism is a reduction in the expression of adhesion molecules on the membrane of the neutrophils (17).

Platelets play an important role in neutrophil diapedesis by forming microthrombi. Ketamine inhibits platelet aggregation and activation (18, 19, 20) but not sufficiently to have any clinical influence on coagulation.

**Ketamine and Cytokine Production**

Cytokins, which are mediators of inflammation play a major role in the immune system. These proteins are divided in two groups: pro- and anti-inflammatory cytokines.

Each inflammatory phenomenon is regulated in space and time by the balance of these two opposed forces (Fig. 3). Pro-inflammatory cytokins initiate inflammation. Anti-inflammatory cytokins temper the initial response. In normal circumstances, the resultant of these two forces guides the body to the resolution of inflammation and healing of the wounded tissues. If uncontrolled, cytokine production can lead to excess or lack of inflammation with its subsequent consequences. The most studied cytokins and their action are summarized in Table 2.

Ketamine influence the immune response by interfering with the cytokine balance. This influence was first described in 1994 (21). Ketamine reduces TNF-α production in mice immune-stimulated with lipopolysaccharide (LPS). This intracellular protein activates the transcription of the genes coding for cytokine production. TNF-α is the first cytokine to be produced, followed by as well pro-inflammatory as anti-inflammatory cytokins. All these factors interact with each other. The end-product of this complicated loop system is the immune response to aggression. The imbalance between pro- and anti-inflammatory cytokines correlates with the heaviness of the immune response.

![Fig. 3](image)

**Table 2**

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Inflammatory action</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α/IL-1</td>
<td>pro</td>
<td>stimulating the cytokine production</td>
</tr>
<tr>
<td></td>
<td></td>
<td>fever</td>
</tr>
<tr>
<td>IL-6</td>
<td>pro</td>
<td>enhancing adhesion molecule production by endothelium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ACTH and cortisol production</td>
</tr>
<tr>
<td>IL-8</td>
<td>pro</td>
<td>stimulating the hepatic production of inflammatory protein</td>
</tr>
<tr>
<td>IL-10</td>
<td>anti</td>
<td>Stimulation neutrophile diapedese</td>
</tr>
<tr>
<td></td>
<td></td>
<td>phagocytosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>free radical production</td>
</tr>
<tr>
<td></td>
<td></td>
<td>lowers the cytokinie production</td>
</tr>
</tbody>
</table>

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immunostimulation, ketamine has important inhibitory effects on cytokine production (reduction of TNF-α and IL-6). In the post-group (2 hours post-immunostimulation), the effect was less but still significant (reduction of IL-6, no effect on TNF-α). The authors conclude to a post-stimulation immunomodulatory effect of ketamine even if weaker than if administered pre-stimulation. Also interesting, the study showed a significant reduction of acidosis and hypotension in the animals receiving ketamine in comparison with the control group.

The immunomodulatory effects of ketamine have also been described in human beings in vivo. Extracorporeal circulation is known to induce the cytokine cascade. In a study based on patients undergoing cardiac surgery (27), the administration of 0.25 mg/kg of ketamine at induction of anesthesia was sufficient to reduce the production of IL-6. This reduction in IL-6 is still present seven days postoperatively. The same observations were made by administering 0.5 mg/kg (28) with a greater effect on the IL-6 production, which resulted in a lower CRP level postoperatively. The same was experienced in a pediatric population (29). In this setting, ketamine did not influence the cytokine cascade. This difference is probably due to systematic administration of steroids in the protocol used in this study.

One study was also made in the setting of liver transplantation (30, abstract) showing a reduction of TNF-α and IL-6 after administration of ketamine. The IL-10 levels were not affected.

Let’s now move to the step preceding cytokine cascade, which is nuclear factor kappa-B production (NFκ-B) (Fig. 3). NFκ-B is an intracellular protein activating the transcription of genes coding for cytokine production. Ketamine inhibits this nuclear factor. In LPS immunostimulated mice, ketamine reduces the expression of NFκ-B (30). This study also underlines two important facts. The first one is that immunomodulation by ketamine is dose dependent. The second one is that ketamine exerts immunomodulatory effects only in the presence of immunostimulation.

The effects of ketamine on NFκ-B expression are also observed when ketamine is administered after immunostimulation (31). This last observation strengthens the idea that ketamine exerts not only a preventive immunomodulatory effect but also an active role when inflammation is already initiated.

Finally also the endothelium produces cytokins. Ketamine has no influence on the endothelial cytokine production (32). All these data’s are summarized in table 3.
To understand the anti-inflammatory mechanism of ketamine, we need to focus on the immunomodulatory properties of another group of mediators: catecholamins. Catecholamines have anti-inflammatory properties. In human endotoxin models, epinephrine inhibits TNF-α production and potentiate anti-inflammatory cytokine IL-10 (33). Norepinephrine inhibits TNF-α and IL-6 production in a gram negative septic model (34).

By stimulating the β2 receptor, catecholamines stimulate the release of adenosine which is known for its anti-inflammatory properties (35, 36). Adenosine stimulates the A2A receptor activating cyclo-oxygenase-2 (COX-2). This enzyme produces prostaglandins such as PGE2. Prostaglandin E2 is a powerful inhibitor of leucocyte function (37, 38, 39, 40). Later, in the resolution phase of inflammation, COX-2 contributes to the production of PGD2, which stimulates the release of anti-inflammatory cytokins (43) by mononuclear cells.

Ketamine interacts with the catecholaminergic system by stimulating the release of catecholamins and inhibiting their reuptake. It may seem realistic to postulate that the anti-inflammatory effects of this drug are mediated by the catecholaminergic receptor. Indeed, antagonizing the A2A receptor blocks the anti-inflammatory effects of ketamine (41, 42). According to this, ketamine may use the A2A-COX2-prostaglandine pathway to modulate inflammation.

### Table 3

Summary of the cited studies concerning the effect of ketamine on cytokine production

<table>
<thead>
<tr>
<th>Subject</th>
<th>Authors</th>
<th>Setting</th>
<th>Population</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>NK-KB production</td>
<td>Sakai et al. (11)</td>
<td>in vitro/in vivo</td>
<td>mice</td>
<td>Reduction of nf-kb expression</td>
</tr>
<tr>
<td></td>
<td>Sun et al. (12)</td>
<td>in vivo</td>
<td>rats</td>
<td>Reduction of nf-kb expression</td>
</tr>
<tr>
<td></td>
<td>Sun et al. (16)</td>
<td>in vitro</td>
<td>monocytes</td>
<td>Reduction of nf-kb activation</td>
</tr>
<tr>
<td></td>
<td>Min et al. (13)</td>
<td>in vivo</td>
<td>rats</td>
<td>Reduction of nf-kb activation</td>
</tr>
<tr>
<td>Cytokine production</td>
<td>Takenaka et al. (2)</td>
<td>in vivo</td>
<td>mice</td>
<td>Reduction of tfn-alpha</td>
</tr>
<tr>
<td></td>
<td>Larsen et al. (3)</td>
<td>in vitro</td>
<td>human monocytes</td>
<td>Reduction of tfn-alfa en IL-1</td>
</tr>
<tr>
<td></td>
<td>Kawasaki et al. (4, 5)</td>
<td>in vitro</td>
<td>human blood</td>
<td>Reduction of tfn-alfa, IL-6 and IL-8</td>
</tr>
<tr>
<td></td>
<td>Taniguchi et al. (6)</td>
<td>in vivo</td>
<td>rats</td>
<td>Reduction of tfn-alfa and IL-6</td>
</tr>
<tr>
<td></td>
<td>Taniguchi et al. (7)</td>
<td>in vitro</td>
<td>rats</td>
<td>Reduction of the IL-6/IL-10 ratio</td>
</tr>
<tr>
<td></td>
<td>Royblat et al. (8)</td>
<td>in vivo</td>
<td>humans</td>
<td>Reduction of IL-6</td>
</tr>
<tr>
<td></td>
<td>Bartoc et al. (9)</td>
<td>in vivo</td>
<td>humans</td>
<td>Reduction of IL-6</td>
</tr>
<tr>
<td></td>
<td>Yang et al. (21)</td>
<td>in vivo</td>
<td>humans</td>
<td>Reduction of tfn-alfa and IL-6</td>
</tr>
<tr>
<td></td>
<td>Takaono et al. (15)</td>
<td>in vitro</td>
<td>human monocytes</td>
<td>no effect on IL-6 an IL-10</td>
</tr>
<tr>
<td></td>
<td>Zahler et al. (14)</td>
<td>in vitro</td>
<td>human endoth/neutroph.</td>
<td>no effect on cytokine production</td>
</tr>
</tbody>
</table>

**Mechanism of the Anti-Inflammatory Properties of Ketamine**

As mentioned earlier, ketamine does not interact directly with the catecholaminergic receptor. It stimulates the release of catecholamins by acting on the nucleus of the tractus solitarii. According to the fact that the influence of the nucleus tractus solitarii is absent in studies made in vitro, the action of ketamine on adenosine is totally independent of the β2 receptor. Ketamine joins the immunomodulatory mechanism of catecholamine downstream the catecholaminergic receptor (Fig. 4).

![Fig. 4. — Adenosine stimulates COX-2, producing different prostaglandins. These prostaglandins plays a varying role depending of the location and time of production. According to this, prostaglandin action vary from stimulating local production of cytokines (pro-inflammatory) to inhibition of the leukocyte function (anti-inflammatory). Ketamine stimulates adenosine production without interfering with the catecholaminergic receptor.](image-url)
Prostaglandins are very versatile actors of inflammation. The same prostaglandin can have a diametrically opposed action in function of the localisation or genesis in inflammation. In the past PGE2 which has been described as inhibiting neutrophils, but is also known to have pro-inflammatory properties by stimulating NFkB production by the endothelium (42). COX-2 has also pro-inflammatory properties by inactivating IkB-α which is an inhibitor of NFkB expression (43). The endothelial COX-2 and the underlying PGE2 production play a pro-inflammatory role locally which is mandatory to initiate the healing processes. This local action of COX-2 is totally opposed to its anti-inflammatory effect on leucocytes.

This duality of action of COX-2 is of major importance. Indeed, non steroidal anti-inflammatory drugs (NSAID) are used in current practice to reduce local inflammation by inhibiting COX-2, by limiting the action of local prostaglandins. But this inhibition of COX-2 has diametrically opposed effects on leucocytes. COX-2 is an activator of leucocytes. Ketamine promotes a different anti-inflammatory effect than an NSAID. By inhibiting COX-2, ketamine blunts the activation of neutrophils without interfering with the local processes. It is confirmed by the fact that ketamine does not have any influence on the endothelial production of cytokins (14).

This makes ketamine very original in the field of anti-inflammation. Ketamine is not efficient in relieving local symptoms associated with inflammation, but it works as a regulator, avoiding the exacerbation of the systemic inflammatory response.

**Ketamine and NO production**

Nitric oxide is a mediator of the inflammatory response. In the setting of inflammation, NO is produced by the inducible form of NO synthetase (iNOS), which is stimulated by pro-inflammatory cytokins. In this context, NO is cytotoxic on microorganisms and tumor cells.

Ketamine inhibits NO production. In vivo studies it has been observed that ketamine administration reduces NO production in immunostimulated macrophages (44, 45). This effect is dose- and time-dependent (45). The action of ketamine on macrophages confirms the early influence of this drug on the inflammatory process. Other NMDA antagonists do not influence NO production, which makes obvious that the inhibitory effect of ketamine is not dependent of this receptor.

It is important to keep in mind that nitric oxide interferes also with regulation of inflammation. In fact, when stimulated, NO production inhibits the further transcription of NFkB (46, 47), which constitutes a novel negative feedback loop. By this, limiting NO production implies loss of autoregulation of the inflammation.

**Immunomodulatory effect of ketamine on the neuro-endocrine axis**

The inflammatory reaction and immune system are influenced by neuro-endocrine factors. The hypothalamo-pituitary axis (HPA) regulates adrenal activity and corticosteroid production. Studies made on healthy volunteers showed that ketamine stimulates the HPA axis and cortisol production (48, 49). Other NMDA antagonists do not (49). The exact mechanism of interaction with the HPA axis is not known but the previously discussed interactions with the catecholaminergic system and prostaglandin production could be a part of the explanation.

Although the NMDA receptor doesn’t seem to be directly involved in the interaction between ketamine and HPA axis, interesting links are observed. Cocaine has stimulating effects on cortisol production. This effect is mediated by the NMDA receptor (50). In addicted people, ketamine is often associated to cocaine. The effects of this association have been described in rats (51). Paradoxically, ketamine blunts the stimulating effects of cocaine on ACTH and cortisol production. Which means that ketamine is a “pro-inflammatory” drug when associated with cocaine. This observation is not relevant in healthy subjects, but has to be considered in addicted people.

**Effect of ketamine on the vagal nerve**

The vagal nerve is known to have anti-inflammatory properties. Acetylcholine released by the vagal nerve interacts with the α7 subunit of the nicotinic receptors of macrophage. The vagal nerve is under control of the nucleus tractus solitarii which is an important relay concerning vagal reflexes, hemodynamic and gastro-intestinal regulation. In this nucleus, glutamate interacts with the NMDA receptor and stimulates the vagal nerve (52, 53).

By antagonizing the NMDA receptor, ketamine acts as an inhibitor of the vagal nerve (54) and blunts its anti-inflammatory properties. The influ-
ence of the vagal nerve on the inflammatory process is very limited. According to this, the influence of ketamine on the vagal nerve is of restricted importance concerning regulation of inflammation.

Finally, we would like to remind that ketamine also interacts with the cholinergic receptor. Direct action of ketamine on the nicotinic receptor of macrophage has not been studied yet.

**Ketamine and apoptosis**

Programmed cell death seems to be implicated in multiple organ failure, systemic inflammatory response syndrome and sepsis. The exact role of apoptosis is not clear yet. In the setting of local damage, the endothelium undergoes massive apoptosis, which initiate a pro-inflammatory and pro-coagulant cascade. On the other hand, in septic states, neutrophils seem to be resistant to apoptosis, keeping them longer active on sites of inflammation.

Without going into more details, it can only be confirmed that ketamine enhances apoptosis of nervous cells in the developing brain (55, 56, 57). The effect of ketamine on inflammatory cell apoptosis has not been studied yet.

Ketamine may also have inhibitory effect on apoptosis using a different mechanism. Pro-inflammatory cytokins and particularly Tnf-α are major activators of apoptosis (58). According to its inhibitory effect on Tnf-α production (21, 26, 30), ketamine may possibly reduce apoptotic phenomenon in the setting of inflammation. This hypothesis also has not investigated yet.

**Ketamine and immunoparalysis**

Critical illness is associated with a high risk of secondary infection. In these patients, the immune system seems blunted. In fact, it is observed that, after having been heavily solicitated by a primary insult, the immune system seems to be temporally paralysed. Which makes it less responsive to a secondary insult. This phenomenon is called immunoparalysis (59). This state of "immunodeficiency" is correlated with enhanced production of Interleukine-10. High doses of IL-10 blunt expression of the Human Leucocyte Antigen complexes (HLA-DR) on the surface of monocytes, making recognition of pathogenic antigen more difficult.

This phenomenon could be a part of explanation to the higher rate of infection seen with prolonged administration of thiopentone which enhance IL-10 levels in the setting of inflammation (65).

Ketamine reduces IL-10 levels after immunostimulation (24). By this, ketamine may theoretically reduce the risk of infection due to immunoparalysis. This hypothesis has not been investigated yet.

**Immunomodulation by Ketamine : Benefits and Limits**

Ketamine offers important immunomodulatory properties. This drug is not an anti-inflammatory agent but has to be considered as an anti-proinflammatory drug:

"Prevention of an exacerbated inflammatory response without impeding with local inflammation".

By this, ketamine keeps local processes like cicatrisation and pathogen eradication possible. At the other hand, ketamine softens the systemic and potentially harmful effects of inflammation. Considering this, anti-proinflammation contributes to the recovery of homeostasis by optimising the inflammatory response. But what are the consequences in terms of morbidity/mortality?

In a study made on septic mice (60), ketamine administration is associated with the following positive effects: optimisation of oxygen transport, reduction in metabolic acidosis and hepatic injury, which result in lower mortality in the ketamine group (40% vs 92%).

The correlation between levels of circulating cytokines and mortality is well described. In a study made on septic rats (61), administration of ketamine was associated with a significant reduction of circulating cytokins, which was associated with a reduction of mortality in the group receiving ketamine (43% versus 73% in the control group). In this study, ketamine was associated after infection which confirms that ketamine not only prevents, but also smoothen excessive inflammatory responses.

In another study based on severely burned mice (62), Ketamine did not improve survival in severely burned mice. The only positive effects of ketamine on survival were found when a septic state was associated with the burn injuries. However, other authors (63) reported better survival rates in severely burned mice sedated with ketamine in comparison with midazolam-fentanyl.

These effects on morbidity/mortality are dose-related. Taniguchi et al. (64) reported a lower mortality rate in septic rats by administrating 10 mg/kg
(0% mortality) in comparison with 5 and 20 mg/kg (respectively 48 and 32% mortality). The mortality rate in the control group was 92%.

These results are very encouraging, but have to be confirmed in further trials.

All these data’s are summarized in table 4.

**Table 4**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study pop.</th>
<th>Studied drugs</th>
<th>Effect on mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shaked et al.</td>
<td>rats with Ge-sepsis</td>
<td>Ketamine vs NaCl 0,9%</td>
<td>49% vs 73%</td>
</tr>
<tr>
<td>Gurfinkel et al.</td>
<td>Mices with burns</td>
<td>ketamine versus midaz + fenta</td>
<td>no differences</td>
</tr>
<tr>
<td></td>
<td>Mices with burns + sepsis</td>
<td>ketamine versus midaz + fenta</td>
<td>54% vs 87%</td>
</tr>
<tr>
<td>Neder Mey et al.</td>
<td>Mices with burns</td>
<td>Ketamine versus midaz + fenta</td>
<td>50% vs 85%</td>
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<tr>
<td>Koga et al.</td>
<td>Mices with burns</td>
<td>Ketamine vs NaCL 0,9%</td>
<td>40% vs 92%</td>
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</table>

**DISCUSSION**

The immune system is very complex. The inflammatory response consists of a large number of components interacting with each other, and evolving in space and time. An overwhelming inflammatory reaction is paired with devastating effects ranging from loss of local homeostasis till irreversible tissue injury.

Since many years, research has been focused on developing anti-inflammatory agents which have proven their efficacy but also their limits. NSAID’s are very useful in relieving local symptoms of inflammation (pain, edema,...) but their long term use may be responsible of maintaining a highly inflammatory state by keeping the neutrophils activated. Corticosteroids are potent anti-inflammatory drugs, but have negative effects on host defences and local healing processes. New molecules have been developed in order to control the inflammatory response in the setting of critical illness. But up to now, none of the studies performed have reported a significant positive effect of these new drugs on mortality in the setting of severe inflammatory responses. The reasons why these researches all failed up to now are not clear. But one basic principle seems evident:

The inflammatory response is a physiological and necessary phenomenon which is an active actor of homeostasis. Anti-inflammatory drugs act by blocking this adaptive response to stress. Considering this, the main focus should be on trying to prevent exacerbation of inflammation rather than blocking it: this is anti-proinflammation.

Ketamine is an immunomodulatory agent acting in synergy with inflammation. It works as an anti-proinflammatory drug. Ketamine avoids the extension and exacerbation of inflammation without blunting the local processes. By this, ketamine has to be considered as a drug that optimizes inflammation in order to restore homeostasis.

Ketamine acts at different levels of the inflammatory response. Major effects of ketamine are due to its influence on cytokine balance. It implies that ketamine interferes very early with the inflammatory response. The effects of ketamine are more pronounced when given before immunostimulation. But the immunomodulatory effects are still significant when given post-immunostimulation. According to this, ketamine not only prevents exacerbation of inflammation but also modulates inflammation when already initiated. This last property makes ketamine very useful in elective situations (operating room) but also in unexpected situations (admission to ICU).

The action on the cytokine balance is of high interest. Indeed, in the last years, several reports pointed out the important role of cytokine balance in the genesis of metabolic and endocrine disregulation in the setting of critical care. By modelling cytokine production, ketamine may potentially reduce these adverse effects.

The immunomodulatory effects of ketamine are only described in the presence of immunostimulation. In the absence of a stress situation, ketamine has no effect on cytokine balance. According to this, ketamine has immunomodulatory properties without being immunosuppressive.

All these positive data have to be confronted with three remarks.

First of all, it is important to keep in mind that inflammation is a ‘defense’ process. Modulating inflammation potentially enhances the risk of infection. Moreover, up to now it is difficult to predict if the inflammatory response of an organism is appropriate, excessive or insufficient. This makes it very hard to know in which organism, when, and in
which situation, immunomodulation would be interesting.

The second remark concerns the dynamic and complex aspect of inflammation. Each mediator of inflammation may have diametrically opposite actions in function of its site and time of production. The immunomodulatory effects of ketamine are potentially variable in function of space and time. However, the results presented in this review seems to support a clearly positive and encouraging effect of ketamine on morbidity-mortality in the setting of inflammation.

The last remark concerns the multiple feedback loops by which inflammation regulates itself. Interfering with inflammation implies also interfering with the autoregulation processes. By this, blunting inflammation also blunts downregulation of inflammation, which may be contradictory.

CONCLUSION

In conclusion, ketamine, at very low doses (0.25 mg/kg), may be a promising drug which may limit and even prevent exacerbated inflammation without impeding with local healing processes. At this dosage, adverse effects are not common (65). This distinctive feature, associated with its hemodynamic, respiratory and sedative properties, makes of ketamine a polyvalent drug in the field of anesthesiology and critical care.

References


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